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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/581,742	06/16/2000	Frederic J. de Sauvage	P1548R1	4676

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EXAMINER
BRANNOCK, MICHAEL T

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 01/04/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/581,742	Applicant(s) DE SAUVAGE ET AL.	
	Examiner Michael T Brannock	Art Unit 1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 November 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-37* is/are pending in the application.

4a) Of the above claim(s) *28-32 and 34-37* is/are withdrawn from consideration.

5)☐ Claim(s) *2,3 and 23* is/are allowed.

6)☐ Claim(s) *1,4-7,9-19,21,22,24-27 and 33* is/are rejected.

7)☐ Claim(s) *8 and 20* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of Application: Claims and Amendments

Applicant is notified that the amendments put forth in Paper 4, 3/22/01, have been entered in full. Claims 1-37 are pending.

Claims 28-32 and 34-37 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention there being no allowable generic or linking claim. Applicant's election of Group I, claims 1-27 and 33 in Paper No. 8, 11/2/01, is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Drawings

The subject matter of this application admits of illustration by a drawing to facilitate understanding of the invention, see pages 5-7. Applicant is required to furnish drawings under 37 CFR 1.81. No new matter may be introduced in the required drawing.

Specification

The disclosure is objected to because of the following informalities: The top margins of the specification are small such that holes placed in the margins obscure the text, a substitute specification is required, see MPEP § 601.

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code, see page 8 for example. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4, 5, 6, 9, 10, 21, 25-27 and 33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 4 requires an isolated nucleic acid molecule "comprising DNA hybridizing to the complement of ..." . This phrase is confusing because it is unclear if the claimed nucleic acid molecule must be in a hybrid with "the complement of" or only capable of forming a hybrid with "the complement of". Further, it is well known in the art that polynucleotides need not be 100% complementary to form hybrids, thus the term "hybridizing" is a relative term which does not indicate the relative degree of relatedness between the two polynucleotides – this degree of relatedness would determine the bounds of the claimed polynucleotide; thus the metes and bounds of the claim cannot be determined.

Claims 5 and 6 recite the phrase "the same mature polypeptide". This phrase is confusing for two reasons: (1) it is unclear what additional limitations the word "same" places on the claim and (2) it is unclear what limitations the word "mature" places on the claims. The phrase "mature polypeptide" is recognized in the art to mean a polypeptide that has completed all post-transnational processing, yet the specification has not put forth exactly what is considered to be

the post-transitional processing of the instant polypeptide that makes it mature. Therefore, the metes and bounds of the claim cannot be determined.

Claims 9 and 21 recite the phrase "scoring at least 80% positives", yet there is no art-recognized definition of this phrase that definitively sets forth what is positive and what is not, and nor is such a definition provided in the specification – such that one skilled in the art would be reasonably appraised of the metes and bounds of the claim. At page 8, the specification appears to address the use of the term "positives" in the context of sequence comparisons but does not clarify how the "% value of positives" is calculated nor how this value specifically relates to the phrase "scoring at least 80% positives".

Claims 4 and 24 require that the nucleic acid hybridize under stringent conditions. The term "stringent conditions" is confusing because it is a relative term and encompasses conditions of varying degrees of stringency - such conditions determining the bounds of the claim. However, the art does not provide an unambiguous definition of the term "stringent conditions" and neither is such a definition given for the term in the specification which puts forth the metes and bounds of the claim Applicant is seeking protection for. At pages 9 bridging 10, the specification defines the term only by way of examples, and it is unclear if each of the recited conditions produce the same degree of stringency for hybridizations between the recited polynucleotides. It is suggested that the claim recite the actual conditions that applicant considers to be stringent, i.e., salt concentration and temperature conditions of incubations and washes.

Claim 22 recites the phrase "or a fragment thereof". This phrase acts as an ambiguous modifier in the sentence because it is unclear if the phrase is meant to apply to "An isolated

hSu(fu) polypeptide" or to "the sequence of amino acid residues from 1 to about 433 of Figure 1", or to both – such distinction would determine the bounds of the claim. If Applicant deems it proper, one way to obviate this for part of the rejection would be to replace the phrase "or a fragment thereof" with the phrase "or a fragment of said polypeptide".

Claims 25-27 require an "hSu(fu) polypeptide". The recited term "hSu(fu) polypeptide", without reference to a specific sequence identifier, is indefinite because the instant specification does not identify that material element or combination of elements which is unique to, and therefore, definitive of "hSu(fu) polypeptide", see pages 7-8. An artisan cannot determine what limitations are placed upon a claim by the presence of this term alone.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4, 7, 9-19, 21, 22, 24-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for polynucleotides comprising a polynucleotide which encodes a polypeptide of having the amino acid sequence of SEQ ID NO: 2, or which encode polypeptides consisting of antigenic fragments of SEQ ID NO: 2, does not reasonably provide enablement for polynucleotides that encode amino acid sequence variants of SEQ ID NO: 2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims encompass polypeptide variants of SEQ ID NO: 2 and polynucleotides encoding polypeptide variants of the polypeptide of SEQ ID NO: 2, i.e. substitutions, deletions or insertions in a protein corresponding to SEQ ID NO: 2, yet the specification has not provided sufficient guidance as to how to make and use the claimed variant polypeptides which are not 100% identical to the polypeptide of SEQ ID NO: 2, but which still retain a desired property of the polypeptide of SEQ ID NO: 2.

The specification has failed to teach one of skill in the art which amino acid substitutions, deletions or insertions to make. Furthermore, the Applicant has not provided guidance as to what properties of the allelic variants or sequence variants of the protein corresponding to SEQ ID NO: 2 might be desired nor any guidance as to which amino acid substitutions, deletions or insertions to make to achieve any desired property. Applicant has not defined a difference in structure or difference in function between the protein corresponding to SEQ ID NO: 2 and variants of said protein. If a variant of the protein corresponding to SEQ ID NO: 2 is to have a structure and function similar to the protein corresponding to SEQ ID NO: 2, then the specification has failed to teach one of skill in the art which amino acid substitutions, deletions or insertions to make that will preserve the structure and function of the protein corresponding to SEQ ID NO: 2.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the

sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Bowie et al., 1990, Science 247:1306-1310, especially p.1306, column 2, paragraph 2). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins (e.g. pg 16), this is not adequate guidance as to the nature of active variants that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity.

Due to the large quantity of experimentation necessary to generate the infinite number of variants required by the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the

effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim 33 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claim requires an anti-sense antagonist of hSu(fu), yet the specification discloses no antisense nucleic acids which, according to an art accepted definition, repress gene expression by hybridizing to target mRNA and thereby inhibiting its translation and decreasing cellular levels of the protein which the gene encodes (see Milligan, J.F. *et al., J. Med. Chem.* 36:14(1923-1937)1993, page 1923, 2nd paragraph). The prior art discloses no antisense sequences complementary to an hSu(fu) encoding nucleic acid that would inhibit translation. There is no guidance or examples to help one skilled in the art to predict which of the multitude of antisense nucleic acids encompassed by the claim would inhibit translation. Designing an antisense nucleic acid requires consideration of, for example, nucleic acid length, complementarity to non-hSu(fu) polynucleotides, and which regions of the polynucleotide must be bound by the antisense nucleic acid. Milligan *et al.* point out many difficulties in producing functional antisense nucleic acids, which include: unpredictability in determining the accessibility of a RNA target site because the accessibility depends on RNA secondary structure which cannot be accurately modeled (see page 1924, last paragraph); conflict between sequence specificity and affinity of the antisense nucleic acid for the target RNA because increasing nucleic acid length

increases specificity up to a point at which the affinity for related non-target sequences increases, leading ultimately to a decrease in specificity (see page 1926, 2nd paragraph); and nuclease degradation of the antisense oligonucleotide (see page 1930, 2nd paragraph). While the method of making an antisense nucleic acid is routine in the art, the unpredictability inherent in the design of one which can inhibit translation would result in undue experimentation in order to make the invention as claimed.

Claims 1, 4, 7, 9-19, 21, 22, 24-27 and 33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification discloses a polynucleotide of SEQ ID NO: 1 encoding a polypeptide of SEQ ID NO: 2, yet the claims encompass polynucleotides and polypeptides not described in the specification, e.g., sequences from other species, mutated sequences, allelic variants, anti-sense nucleic acid molecules, or sequences that have a recited degree of identity. None of these sequences meet the written description provision of 35 U.S.C. 112, first paragraph. Although one of skill in the art would reasonably predict that these sequences would or could exist, one would not be able make useful predictions as to the nucleotide positions or identities of those sequences based on the information disclosed in the specification.

A genus claim may be supported by a representative number of species as set forth in Regents of the University of California v Eli Lilly & Co, 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). A description of a genus of cDNAs may be achieved by means of a

recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. The instant specification discloses, however, a single isolated polynucleotide sequence SEQ ID NO: 1 . No activity is set forth for the additional sequences encompassed by the claims. Further, even if the disclose sequence were definitive of a genus with a specified function, the instantly claimed genus is not so limited and the prior art does not provide compensatory structural or correlative teachings to enable one of skill to identify/obtain the polynucleotides encompassed.

With the exception of the of the polynucleotide of SEQ ID NO: 1 and the polypeptide of SEQ ID NO: 2, the skilled artisan cannot envision the detailed chemical structure of the encompassed variants. Therefore, only the polynucleotide of SEQ ID NO: 1 and the polypeptide of SEQ ID NO: 2, and polynucleotides or polypeptides consisting of fragments thereof, and polynucleotides or polypeptides consisting of fragments thereof and heterologous nucleic acid or amino acids sequences (e.g. vector or tag sequences), but not the full breadth of the claims meet the written description provision of 35 U.S.C. §112, first paragraph.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 4 and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by GenBank accession number AA061391, Marra et al., 03-Feb-1997.

GenBank accession number AA061391 disclose an isolated nucleic acid molecule comprising DNA that is 94.9% identical to the instant SEQ ID NO: 1 from positions 189 to 463 of SEQ ID NO: 1 (see attached sequence alignment) and would therefore be expected to hybridize to the complement of the nucleic acid having the sequence of nucleotide positions from about 74 to about 1372 of SEQ ID NO: 1 (as is required by claim 4) and to be produced by hybridizing a test molecule under stringent conditions with a DNA molecule encoding a hSu(fu) polypeptide, e.g. SEQ ID NO: 1 (as is required by claim 10).

Allowable Subject Matter

Claims 8 and 20 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claims 2, 3 and 23 are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael T Brannock whose telephone number is 703 306-5876. The examiner can normally be reached on Monday-Friday, 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on 703 308-6564. The fax phone numbers for the organization where this application or proceeding is assigned are 703 308-4242 for regular communications and 703 308-0294 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 308-0196.

MB
January 2, 2002

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